PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JAF-PB60385	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/EP2004/007666	International filing date *(day/month/year)* 08.07.2004	Priority date *(day/month/year)* 11.07.2003

International Patent Classification (IPC) or national classification and IPC
A61K9/14

Applicant
GLAXO GROUP LIMITED et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.04.2005	23.11.2005

Name and mailing address of the international preliminary examining authority:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Muller, S

Telephone No. +31 70 340-2080

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/007666

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-17 as originally filed

   Claims, Numbers

   1-19 received on 30.06.2005 with letter of 28.06.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/007666

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☒ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   - ☐ the entire international application,
   - ☒ claims Nos. 18, with respect to industrial applicability

     because:

   - ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
   - ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:
   - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
   - ☒ no international search report has been established for the said claims Nos. 18, with respect to industrial applicability
   - ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

   - ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   - ☒ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-19
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-17,19
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item II

Priority

Earlier WO application WO 03/088943 D1 published on 30 October 2003 claims the priority date of 13 april 2002. It discloses (see page 2, lines 22-28) a pharmaceutical composition comprising an active ingredient (similar to those of the present application) and a carrier (lactose). Magnesium stearate, which improves the stability performance of such compositions, may be further added (see page 7, line 34 - page 8, line 4).
The subject matter of claims 11-13,17-19 is therefore explicitely anticipated in D1.
It is also stressed that **a newly discovered technical effect** (such as chemical interaction or chemical degradation) does not confer novelty on a claim directed to the use of a known substance for a **known non-medical purpose** (improved stability) if the newly discovered technical effect already underlies the known use of the known substance. Since magnesium stearate is already known as a stabiliser for the claimed compositions, the subject-matter of claims 1-10,14-16 is implicitely anticipated in D1.
The application GB0316341 (date of filing 11 July 2003) to which the priority claim of the present application is directed, is therefore not the application disclosing for the first time some of the subject-matter of the present EP application. As some of the subject-matter as described above was disclosed in a still earlier application D1 originating from the same applicant (GLAXO GROUP LTD), the application GB0316341 is in fact not the "first application" in the sense of Article 8 PCT. Therefore, the priority claim is invalid for the subject-matter already disclosed in the still earlier application D1 and document D1 will be considered as forming part of the prior art.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

For the assessment of the present claim 18 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not

recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Cited Documents

The following documents are referred to in this communication:

D1: WO 03/088943 A (BULSARA PALLAV ARVIND ; GLAXO GROUP LTD (GB); ROCHE TREVOR CHARLES (GB) 30 October 2003 (2003-10-30)

D2: WO 00/28979 A (SKYEPHARMA AG ; MUELLER WALZ RUDI (DE); KELLER MANFRED (DE)) 25 May 2000 (2000-05-25)

2. Novelty

A newly discovered technical effect (such as chemical interaction or chemical degradation) does not confer novelty on a claim directed to the use of a known substance for a **known non-medical purpose** (improved stability) if the newly discovered technical effect already underlies the known use of the known substance.

D1 discloses (see page 2, lines 22-28 and page 7, line 34 - page 8, line 4) a pharmaceutical composition comprising an active ingredient (similar to those of the present application) and a carrier (lactose). Magnesium stearate, which improves the stability performance of such compositions, may be further added. The subject-matter of claims 1-19 is therefore not new (Article 33(2) PCT).

D2 discloses (see examples 1-3) the use of 0,1-2% w/w magnesium stearate for stabilising

a dry powder formulation for inhalation which comprises an active substance (formoterol) and a carrier (lactose). The subject-matter of claims 1-7,9,10,14-19 is therefore not new (Article 33(2) PCT).

3. Inventive Step

Claims 1-19 not being new are also not inventive (Article 33(3) PCT).

4. Industrial applicability

Claim 18 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT). Claims 1-17,19 satisfy the criterion of industrial applicability set forth in Article 33(4) PCT.

PB60385PCT

09 05 2005

(77)

CLAIMS

1. Use of magnesium stearate to inhibit or reduce chemical interaction between an active ingredient substance and a carrier in a solid pharmaceutical formulation, wherein said active ingredient substance is susceptible to chemical interaction with said carrier.

2. Use of magnesium stearate to inhibit or reduce chemical degradation of an active ingredient substance in a solid pharmaceutical formulation comprising the active ingredient substance and a carrier, wherein said active ingredient substance is susceptible to chemical interaction with said carrier.

3. Use as claimed in claim 1 or claim 2 wherein the carrier is a reducing sugar.

4. Use as claimed in claim 3 wherein the carrier is lactose.

5. Use as claimed in any one of claims 1 to 4 wherein the magnesium stearate is present in an amount of from 0.1 to 20% w/w based on the total weight of the composition.

6. Use as claimed in any one of claims 1 to 5 wherein the active ingredient substance is present in an amount of from 0.01% to 50% w/w based on the total weight of the composition.

7. Use as claimed in any one of claims 1 to 6 wherein the drug substance is one which includes the group Ar-CH(OH)-CH_2-NH-R.

8. Use according to claim 7 wherein said drug substance is selected from:

3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl) benzenesulfonamide;
3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl}-amino)heptyl]oxy}propyl)benzenesulfonamide;
4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol and
4-{(1*R*)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol,

or a salt, solvate or physiologically acceptable derivative thereof.

9. Use as claimed in any one of claims 1 to 8 wherein the solid pharmaceutical formulation is for administration by inhalation.

10. Use as claimed in any one of claims 1 to 9 wherein the solid pharmaceutical formulation comprises two or more active ingredient substances.

11. An inhalable solid pharmaceutical formulation comprising (a) an active ingredient substance susceptible to chemical interaction with lactose which active ingredient is selected from:
3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl] oxy}butyl) benzenesulfonamide;
3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl}-amino)heptyl]oxy}propyl)benzenesulfonamide;
4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol and
4-{(1*R*)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol,
or a salt, solvate or physiologically acceptable derivative thereof.
(b) lactose and
(c) magnesium stearate.

12. An inhalable solid pharmaceutical formulation as claimed in claim 11 further comprising one or more of the features described in any one of claims 5 or 6.

13. An inhalable solid pharmaceutical formulation as claimed in claim 11 or claim 12 wherein the active ingredient substance is 3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl] oxy}butyl) benzenesulfonamide; or a salt, solvate or physiologically acceptable derivative thereof, and the carrier is lactose.

14. A method of reducing or inhibiting chemical interaction between an active ingredient substance and a carrier susceptible to chemical interaction, which comprises mixing magnesium stearate with said active ingredient substance and said carrier.

15. A method of inhibiting chemical degradation of an active ingredient substance in a formulation comprising a carrier and an active ingredient substance, which method comprises mixing magnesium stearate with said active ingredient substance and said carrier.

16. A method as claimed in claim 14 or 15 further comprising one or more of the features described in any one or more of claims 3 to 10.

17. Use of an inhalable solid pharmaceutical formulation as claimed in claim 11 to 13 for the manufacture of a medicament for the treatment of asthma, chronic obstructive pulmonary disease (COPD), chronic or wheezy bronchitis, emphysema, respiratory tract infection, upper respiratory tract disease or rhinitis, including seasonal and allergic rhinitis.

18. A method for treating asthma, chronic obstructive pulmonary disease (COPD), chronic or wheezy bronchitis, emphysema, respiratory tract infection, upper respiratory tract disease, or rhinitis, comprising administering to a patient in need thereof an inhalable solid pharmaceutical formulation as claimed in claim 11 to 13.

19. A method of preparing a solid pharmaceutical preparation comprising combining in one or more steps: (a) an active ingredient substance susceptible to interaction with a carrier, (b) a carrier and (c) magnesium stearate.